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DIALYSIS – TRANSPLANTATION

Risk factors for post-transplant tuberculosis

GEORGE THARAYIL JOHN, VISWANATHAN SHANKAR, ABI MOOKANOTTLE ABRAHAM, UMA MUKUNDAN, PAULOSE PUNNAKUZHATHIL THOMAS, and CHAKKO KORULA JACOB

Departments of Nephrology, Biostatistics, and Microbiology, Christian Medical College and Hospital, Vellore, Tamil Nadu, India

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Background. Post-transplant tuberculosis (post-TxTB) occurs in 12 to 20% of patients in India and results in the death of 20 to 25% of those patients. Prospective studies on post-TxTB are few.

Methods. Renal allograft recipients were studied prospectively for 3.1 (0 to 13.9) median (range) years for incidence, manifestations, risk factors, and prognosis for post-TxTB. Kaplan-Meier analysis was used to study the survival rates. The extended Cox proportional model for time-dependent covariates was used to measure the risk factors when the hazard was nonuniform.

Results. Of the 1414 patients considered for inclusion, multiple-transplant subjects ($N = 37$) and patients who developed pre-transplant TB (pre-TxTB; $N = 126$) were excluded from the study. The prevalence of post-TxTB was 13.3% ($N = 166$). The risk of post-TxTB when on cyclosporine (CsA) therapy was 2.5 ($P = 0.0311$) and 1.9 ($P = 0.0430$) times at ≤6 and ≤12 months, respectively, compared with patients on prednisolone plus azathioprine (PRED + AZA). The risk of post-TxTB in the presence of diabetes mellitus, chronic liver disease, and other co-existing infections [including deep mycoses, cytomegalovirus (CMV), *Pneumocystis carinii* pneumonia (PCP), nocardia] was 2.2 ($P = 0.0011$), 1.7 ($P = 0.0010$) and 2.4 ($P < 0.0001$) times, respectively. Of the 166 patients with post-TxTB, 53 patients died, and of those deaths, 17 (32%) were due to post-TxTB; 11 (65%) of the 17 had co-existing infections. The factors associated with death were HLA mismatches, PRED + AZA immunosuppression, pre- and post-TxTB, diabetes mellitus, post-transplant diabetes (PTDM), and other co-existing infections. The extended Cox model for death as the outcome variable showed the following to be significant risk factors: post-TxTB >2 years ($P = 0.0036$), chronic liver disease >6 years ($P = 0.0457$), PTDM >5 years ($P = 0.0729$), diabetes mellitus ($P = 0.0091$), human lymphocyte antigen match ≤1 antigen ($P = 0.0134$), two to three antigens ($P = 0.0448$), and the presence of other co-existing infections ($P < 0.0001$).

Conclusions. Cyclosporine therapy is associated with early post-TxTB. Diabetes mellitus and chronic liver disease are risk factors for post-TxTB. The occurrence of both pre-TxTB and post-TxTB (>2 years) along with hyperglycemia, liver disease, and other co-existing infections are important risk factors for death.

Key words: renal transplantation, allograft and infection, infection, tubercle bacillus, bacterial infection, India and TB.

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Renal transplantation has been increasingly carried out in developing countries. In the Indian subcontinent, an estimated 4000 renal transplantations take place annually. As reported earlier, infectious complications lead the causes of morbidity and mortality among these patients [1]. Powerful immunosuppression prevents organ rejections at the expense of increasing the incidence of ambient and opportunistic infections. It is estimated that in the last decade, at least 50% of the Indian population above the age of 20 years is infected with the tubercle bacillus and remains at risk for the disease [2]. The prevalence of post-transplant tuberculosis (post-TxTB) in India is reported to be the highest in the world, and the mortality among those afflicted is high at 20 to 25% [3]. However, most data on this important disease are from retrospective or short-term studies.

The present report documents the incidence, distribution, risk factors, and prognosis of post-TxTB in a large cohort drawn from all parts of India and surrounding countries who were followed up prospectively for over a decade at a single center.

All 1414 patients who received a renal transplant during the study period were studied for the outcome analysis. Of this cohort, 126 patients who developed pre-transplant TB (pre-TxTB) and 37 patients who received multiple transplants and had a different risk profile were excluded from the analysis of risk factors for post-TxTB. The mean age of this patient cohort was 32.8 ± 11 (SD) years, and 1033 (82.6%) were males.

METHODS

Patients

From 1986 to 1999, 1414 patients who received a renal transplant at the Christian Medical College and Hospital at Vellore in southern India were prospectively studied. The incidence, distribution, risk factors, and prognosis of post-TxTB were analyzed. Patients received predniso-

lone plus azathioprine (PRED + AZA) immunosuppression until 1989 and thereafter, PRED + AZA + cyclosporine (CsA), or PRED + CsA (CsA at a higher dose) was used. CsA was discontinued in most patients at one year. Monoclonal antibodies were used for treatment of recurrent or refractory rejections from 1994. Mycophenolate mofetil rescue has been used since 1999 for CsA toxicity and for recurrent rejections.

Patients were seen in the center three times weekly for the first two months, twice weekly for the next two months, and once weekly for the fifth and sixth months; then they were seen at 9 and 12 months and whenever necessary. The follow-up was 100% at six months, 80% at nine months, and 90% at one year. Subsequently, a clinic follow-up of 40% and communication with another 25% of patients with a specific need or on an annual basis was possible.

Patients with pre-TxTB ($N = 126$) had a minimum of six weeks of antituberculosis therapy (ATT) prior to transplantation, completed the course at 18 months, and continued lifelong secondary isoniazid chemoprophylaxis.

Post-TxTB was clinically suspected when a patient presented with fever or symptoms of organ involvement. In some instances, post-TxTB was found on routine physical examination. Involvement of the lung was studied with radiographs, sputum, gastric juice [4], or bronchoalveolar lavage specimens. Tissue diagnosis of affected organ or evaluation of exudative effusions was attempted whenever possible these were examined using histopathology, microscopy, and culture.

All patients with post-TxTB were treated with ATT for 18 months and were followed up with lifelong, secondary isoniazid prophylaxis. Until 1990, patients received streptomycin for three months, pyrazinamide for nine months, and ethambutol + isoniazid for 18 months. Rifampicin was used in a few patients on PRED + AZA, doubling the dose of PRED to compensate for cytochrome P-450 induction. Since 1994, ofloxacin has been used for nine months and pyrazinamide for the first three months along with ethambutol and isoniazid. Primary chemoprophylaxis was not used during this period except as part of a trial [5]. Empirical ATT was given when radiological evidence suggested TB or for pyrexia of unknown origin (PUO) when other tests were negative.

Statistical methods

Descriptive statistics, cumulative calendar-year incidence, and actuarial incidence were calculated for post-TxTB. Kaplan-Meier analysis and log-rank statistics were used to study the association between explanatory variables and post-TxTB.

In analyzing the risk factors for the occurrence of tuberculosis and for death, the variables were checked for proportionality assumptions. In the analysis of the occurrence of post-TxTB, immunosuppression violated the assumption of proportionality. In the analysis of factors affecting the outcome, there was a similar violation of proportionality with risk factors for death, namely, post-TxTB, chronic liver disease, and post-transplant diabetes mellitus (PTDM), defined as fasting blood sugar >120 mg/dL and two-hour post-prandial blood sugar >200 mg/dL or two elevated levels of either measurement. These variables were analyzed with extended Cox model for time-dependent covariates using heavy side functions along with the other time-independent variables that were significant at 20% level of significance in the univariate Cox regression model [6]. The data were analyzed using SPSS for Windows software.

Table 1. Demographic features, risk factors and outcome of post-transplant tuberculosis (TB)

Variables	Post-TxTB (%) $N = 166$	No TB (%) $N = 1085$	P value
Age *years*	34.5 (10.3)	32.5 (11.1)	0.0270
Follow-up *years*			
Median, range	1.6 (0.1–11.5)	3.7 (0–13.9)	<0.0001
Sex			
Male	138 (83.1)	895 (82.5)	0.7897
Female	28 (16.9)	190 (17.5)	
Donor age	40.8 (11.7)	40.9 (11.9)	0.9310
Donor sex			
Male	71 (42.8)	496 (45.7)	0.5964
Female	95 (57.2)	589 (54.3)	
HLA match			
≤1	26 (15.7)	143 (13.2)	0.4017
2–3	116 (69.9)	816 (72.5)	
≥4	24 (14.5)	126 (11.6)	
Immunosuppression			
PRED + AZA group	61 (36.7)	286 (26.4)	0.1391
CsA group	105 (63.3)	799 (73.6)	
Chronic liver disease			
Yes	71 (42.8)	251 (23.1)	<0.0001
No	95 (57.2)	834 (76.9)	
Hyperglycemia			
Diabetes mellitus	19 (11.4)	68 (6.3)	0.0017
PTDM	27 (16.3)	127 (11.7)	
No	120 (72.3)	890 (82.7)	
Other co-existing infections			
Yes	30 (18.1)	85 (7.8)	<0.0001
No	136 (81.9)	1000 (92.2)	
Outcome			
Graft loss	10 (6.0)	88 (8.1)	0.0055
Lost to follow-up	16 (9.6)	128 (11.8)	
Renal failure	6 (3.6)	26 (2.4)	
Alive	81 (48.8)	630 (58.1)	
Dead	53 (31.9)	213 (19.6)	

Abbreviations are: PRED + AZA, prednisolone + azathioprine; PTDM, post-transplant diabetes mellitus; CsA group, most received cyclosporine immunosuppression for a year.

RESULTS

Of the remaining 1251 patients, the prevalence of post-TxTB was 13.3% ($N = 166$) over a median (range) follow-up period of 3.1 (0 to 13.9) years. The patient and donor characteristics, risk factors, and outcome are shown in Table 1. The distribution of liver disease, diabetes melli-

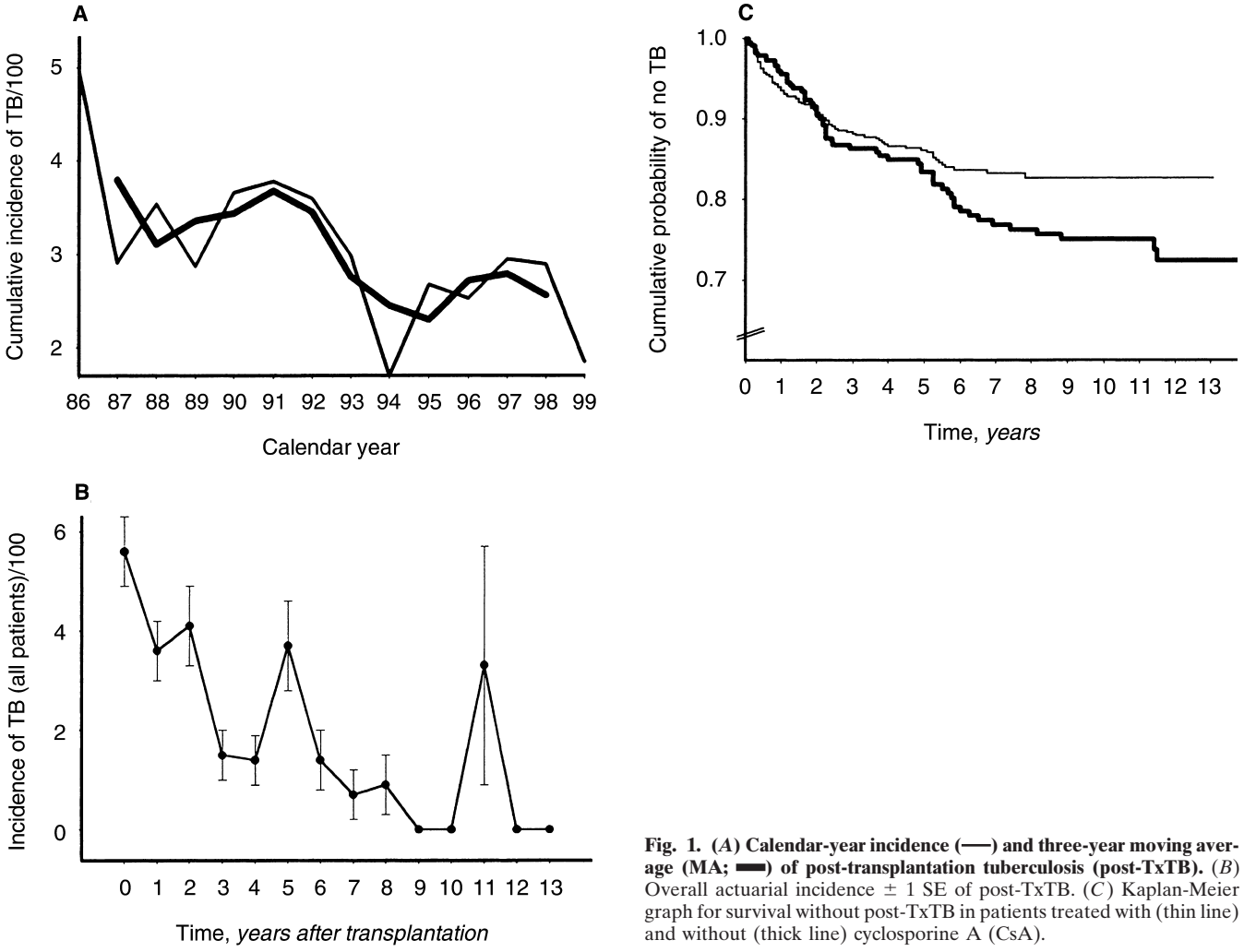

Fig. 1. (*A*) Calendar-year incidence (——) and three-year moving average (MA; ▬) of post-transplantation tuberculosis (post-TxTB). (*B*) Overall actuarial incidence ± 1 SE of post-TxTB. (*C*) Kaplan-Meier graph for survival without post-TxTB in patients treated with (thin line) and without (thick line) cyclosporine A (CsA).

tus, other co-existing infections [deep mycoses, cytomegalovirus (CMV), *Pneumocystis carinii* pneumonia (PCP), nocardia] and the distribution of death was significantly more in patients with post-TxTB (31.9%) as compared with those without the disease (19.6%, $P = 0.0055$). However, the distribution of graft loss or renal failure (creatinine >3.5 mg/dL) was similar in both groups.

The calendar-year incidence of post-TxTB in renal transplant recipients was computed per 100 patients and is shown in Figure 1A. There was a year-to-year variation, and the three-year moving average indicates a lower incidence during the latter half of the study period as compared with 1980s and early 1990s. There is a declining incidence of post-TxTB with the passing years after transplantation (Fig. 1B).

The distribution of lesions of post-TxTB is shown in Table 2. Pleuropulmonary involvement was seen in 48.2% and disseminated tuberculosis in 19.3% of patients. Three fourths of patients had histopathological or microbiological proof of tuberculosis. Empirical ATT was given to 43 (25.9%) patients of whom 26 had a PUO that responded to treatment. The remaining 17 had exudative, lymphocytic effusions, or radiological lesions highly suggestive of TB. In two patients, the diagnosis of post-TxTB was possible only with post-mortem examination. The probability of patients surviving without post-TxTB was 93.5, 86, and 82.6% on CsA immunosuppression and 95.6, 83.4, and

Table 2. Manifestations of post-transplant tuberculosis.

TB location ($N = 166$)	N (%)
Lung and pleura	80 (48.2)
Disseminated	32 (19.3)
Pyrexia of unknown origin	26 (15.7)
Lymph node	8 (4.8)
Skin and soft tissue	7 (4.2)
Intestine	5 (3.0)
Central nervous system	3 (1.8)
Bone	2 (1.2)
Pericardial	2 (1.2)
Urinary tract	1 (0.6)

Table 3. Risk factors for post-TxTB.

Variables	HR	95% CI	*P* value
Age	1.01	1.00–1.03	0.0500
Hyperglycemia			
Diabetes mellitus	2.24	1.38–3.65	0.0011
PTDM	1.12	0.73–1.70	0.6094
No	1.00		
Chronic liver disease			
Yes	1.72	1.24–2.39	0.0010
No	1.00		
Other co-existing infections			
Yes	2.35	1.57–3.54	<0.0001
No	1.00		
Immunosuppression (TDC)			
Cyclosporine ≤6 months	2.45	1.08–5.54	0.0311
Cyclosporine >6 months	0.76	0.52–1.11	0.1539
PRED + AZA	1.00		
Immunosuppression (TDC)			
CsA group 0-12 months	1.85	1.02–3.37	0.0430
CsA group >12 months	0.68	0.45–1.03	0.0693
PRED + AZA	1.00		

Abbreviations are: PRED + AZA, prednisolone + azathioprine; PTDM, post-transplant diabetes mellitus; TDC, time-dependent covariate; CsA group, most received cyclosporine immunosuppression for a year.

Adjusted hazard ratio (HR), 95% confidence interval (CI) and *P* value (time-dependent covariate) are shown.

75% on PRED+AZA at 1, 5 and 10 years, respectively (Fig. 1C).

On examination of the associations of the risk factors for post-TxTB using univariate analysis, age [hazard ratio (HR), 1.02; 95% CI, 1.01 to 1.04, $P = 0.0015$], chronic liver disease (HR, 1.96; 95% CI, 1.44 to 2.67, $P < 0.0001$), diabetes mellitus (HR, 2.31; 95% CI, 1.42 to 3.76, $P = 0.0007$), PTDM (HR, 1.31; 95% CI, 0.86 to 1.99, $P = 0.2025$), other co-existing infections (deep mycoses, CMV, PCP, nocardia; HR, 2.74; 95% CI, 1.84 to 4.06, $P < 0.0001$) and CsA immunosuppression 0 to 12 months (HR, 1.49; 95% CI, 0.83 to 2.69, $P = 0.1839$) were found to be significant. Further multivariate modeling with these variables demonstrated that the risk of post-TxTB in the presence of diabetes mellitus and chronic liver disease was 2.2- and 1.7-fold, respectively. The relative risk of other co-existing infections (deep mycoses, CMV, PCP, nocardia) was 2.4 times in the presence of post-TxTB. The risk of post-TxTB on CsA was 2.5 times at ≤6 months and 1.9 times at 0 to 12 months when compared with patients on PRED + AZA. However, the risk for post-TxTB >12 months on PRED + AZA was 1.5 times as compared with those who had received CsA immunosuppression (Table 3).

The outcome of patients with post-TxTB was studied in comparison with those who did not develop the disease. Of the 166 patients who developed post-TxTB, 53 patients died and of these deaths, 17 (32%) were from post-TxTB. An associated co-existence of other infections (deep mycoses, CMV, PCP, nocardia, and hepatotropic viral infections with chronic liver disease) contributed to the deaths of 11 (65%) of these 17 patients.

Table 4. Distribution of demographic details for patients dead and alive

Variables	Dead (%) *N* = 318	Alive (%) *N* = 1096	*P* value
Age	35.9 (12.4)	32.1 (10.31)	<0.0001
Follow-up *years*			
Median, range	1.5 (0–11.9)	4.0 (0–13.9)	<0.0001
Sex			
Male	253 (79.6)	916 (83.6)	0.1132
Female	65 (20.4)	180 (16.4)	
Donor age	40.2 (12.2)	40.7 (11.9)	0.4390
Donor sex			
Male	154 (48.4)	507 (46.3)	0.4893
Female	164 (51.6)	589 (53.7)	
HLA match			
≤1	63 (19.8)	151 (13.8)	0.0480
2–3	222 (69.8)	809 (73.8)	
≥4	33 (10.4)	136 (12.4)	
Immunosuppression			
PRED + AZA	138 (43.4)	262 (23.9)	<0.0001
CsA group	180 (56.6)	834 (76.1)	
TB			
Pre-transplant TB	32 (10.1)	88 (8.0)	0.0091
Post-transplant TB	59 (18.6)	116 (10.6)	
No	227 (71.4)	892 (81.4)	
Chronic liver disease			
Yes	106 (33.3)	274 (25.0)	0.2343
No	212 (66.7)	822 (75.0)	
Hyperglycemia			
Diabetes mellitus	43 (13.5)	59 (5.4)	<0.0001
PTDM	43 (13.5)	131 (12.0)	
No	232 (73.0)	906 (82.7)	
Other co-existing infections			
Yes	63 (19.8)	70 (6.4)	<0.0001
No	255 (80.2)	1026 (93.6)	

Alive includes lost to follow-up, patients with graft loss and renal failure. Abbreviations are: PRED + AZA, prednisolone + azathioprine; PTDM, post-transplant diabetes mellitus; CsA group, most received cyclosporine immunosuppression for a year.

The distribution of risk factors and demographic details of patients who died and of others are detailed in Table 4. The probability of survival with pre-TxTB was 86.7, 66.7, and 66.7% and with post-TxTB was 92.5, 68.3, and 52.5% at 1, 5, and 10 years, respectively. In comparison, the survival in patients without TB was 91.1, 76.7, and 70.8%, respectively ($P = 0.0091$). On univariate analysis, the factors associated with death were the recipient age (HR, 1.03; 95% CI, 1.02 to 1.04, $P < 0.0001$), HLA ≤1 antigen match (HR, 1.62; 95% CI, 1.06 to 2.47, $P = 0.0236$), PRED + AZA immunosuppression (HR, 1.66; 95% CI, 1.32 to 2.08, $P < 0.0001$), pre-TxTB (HR, 1.37, 95% CI, 0.94 to 1.98, $P = 0.0925$), post-TxTB >2 years (HR, 2.25; 95% CI, 1.50 to 3.37, $P = 0.0001$), chronic liver disease >6 years (HR, 3.33; 95% CI, 1.43 to 7.73, $P = 0.0051$), diabetes mellitus (HR, 2.50; 95% CI, 1.80 to 3.46, $P < 0.0001$), PTDM >5 years (HR, 2.35; 95% CI, 1.17 to 4.73, $P = 0.0165$), and the presence of other co-existing infections (HR, 2.91; 95% CI, 2.21 to 3.84, $P < 0.0001$). Analyzing these time-dependent variables using the extended Cox model for death as the

Table 5. Risk factors for death using the extended Cox model

Variables	HR	95% CI	*P* value
Age	1.03	1.02–1.04	<0.0001
Sex			
Male	0.74	0.56–0.98	0.0341
Female	1.00		
HLA match			
≤1	1.71	1.12–2.61	0.0134
2–3	1.48	1.02–2.14	0.0448
≥4	1.00		
Immunosuppression			
PRED + AZA	1.62	1.27–2.07	0.0001
CsA group	1.00		
Other co-existing infections			
Yes	2.91	2.18–3.87	<0.0001
No	1.00		
TB			
Pre-transplant TB	1.31	0.90–1.90	0.1573
Post-TxTB ≤2 years	0.82	0.54–1.25	0.3649
Post-TxTB >2 years	1.84	1.22–2.78	0.0036
No	1.00		
Chronic liver disease			
Liver ≤6 years	0.79		
Liver >6 years	2.39	0.61–1.04	0.0987
No	1.00	1.02–5.62	0.0457
Hyperglycemia			
Diabetes mellitus	1.66	1.13–2.42	0.0091
PTDM ≤5 years	0.67	0.46–0.99	0.0454
PTDM >5 years	1.91	0.94–3.89	0.0729
No	1.00		

Abbreviations are: HR, adjusted hazard ratio; PRED + AZA, prednisolone + azathioprine; PTDM, post-transplant diabetes mellitus; Post-TxTB, post-transplant tuberculosis; CsA group, most received cyclosporine immunosuppression for a year.

outcome variable, the significant risk factors were post-TxTB >2 years, chronic liver disease >6 years, diabetes mellitus, PTDM >5 years, HLA mismatches, and presence of other co-existing infections (Table 5).

DISCUSSION

The prevalence of post-TxTB in the developed Western nations ranges from 1 to 4% [7, 8], while reports from India show a much higher prevalence. This remarkable difference in prevalence is a result of high endemic TB in India. There is a variation in prevalence within the country, as 11.8% were found in northern India [3], 13.3% in the southern area (present study), and 8.3% in a previous report [9]. This is in part a result of the varying proportion of patients receiving empirical therapy; for example, empirical therapy was reported in 39% of post-TxTB patients [3], while in the present study, 26% patients received empirical therapy. The duration of TB after transplantation in our cohort altered the prevalence of post-TxTB, because the disease incidence declines in the late post-transplant years.

The calendar-year incidence of post-TxTB is important baseline data for practitioners of transplant medicine in developing countries to help the early detection of an unusually high incidence of post-TxTB, occurring due to unusual exposure or risk factors.

The early occurrence of post-TxTB in these patients on CsA has been suggested before [10] and is demonstrated in this large cohort. This occurs due to CsA therapy depressing the lymphocyte proliferation and macrophage function by down-regulating the release of interleukin-2 and tumor necrosis factor-γ [11]. Most patients on CsA who are likely to develop post-TxTB will have developed the disease by six years. After six years, post-TxTB rarely occurs in CsA-treated patients unless there is an unusually heavy environmental exposure. This pattern suggests a process of reactivation of dormant foci of TB. Lymph nodal disease occurs only in a minority, as the disease escapes beyond the confines of the reticuloendothelial system in the immunosuppressed patient.

The risks associated with the development of post-TxTB have so far not been studied systematically. This study with the largest number of affected individuals reported so far shows that diabetes mellitus and chronic liver disease independently increase the risk of developing post-TxTB 1.7 times. The presence of other co-existing infections (deep mycoses, CMV, PCP, nocardia) is an important association. These features mark the individual at risk who, when clinically suspect, warrants more detailed investigations.

The risk of death has been approximately 20 to 25% in a detailed literature review [7] and in a report from India [3]. The death rate depends on the study duration of the cohort following transplantation. Later post-transplant years witness a smaller number of cases of TB but higher death rates. Post-TxTB occurring after two years of transplantation independently carries a 1.8-fold risk of death as compared with patients who did not develop the disease. Post-TxTB that occurs away from medical observation beyond two years is again undetected until the patient is often moribund. In contrast, post-TxTB occurring within the first two years does not increase risk of death.

Tuberculosis occurring two years after transplantation as well as pre-transplant TB are risk factors for death after the transplant, as are diabetes mellitus, PTDM, chronic liver disease, and the occurrence of other coexisting infections such as deep mycoses, CMV, PCP, and nocardia. The hazard of death with chronic liver disease and post-transplant DM varies with time. Chronic liver disease independently increases the risk of death threefold at six years after transplantation. Unabated viral proliferation, hepatic fibrosis, and subsequent liver dysfunction take approximately six years to manifest in our population. Post-transplant DM that occurs five years after transplantation doubles the risk of death. This is related to a period of unrecognized hyperglycemia occurring in some patients, which results in a higher susceptibility and poor response to infections.

These observations are unique to vast developing countries such as India where appropriate medical care is not

available to many patients once they leave the parent hospital. A revisit to the parent hospital with a complication is often delayed due to socioeconomic constraints, vagaries of weather, and nonavailability of surface transport. This aspect underlines the poignancy of the practice of transplant medicine in developing regions. We attempt to refer every patient to competent physicians to ensure early attention in various parts of the country.

Certain factors that increase susceptibility to post-TxTB are important independent risk factors for death as well. Therefore, prevention of chronic liver disease, optimal control of hyperglycemia, and identification of patients at risk are as important as early diagnosis and treatment of post-TxTB, and this is even more important during the later years.

Reprint requests to George T. John, M.D., Department of Nephrology, Christian Medical College and Hospital, Vellore 632004, India. E-mail: george@cmcvellore.ac.in

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